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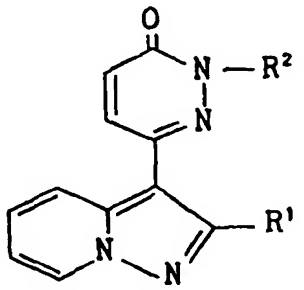

(I)

(57) Abstract

A pyrazolopyridine compound of formula (I),: wherein R^1 is a phenyl having one or two substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, hydroxy, lower alkoxy and ar(lower)alkoxy; and R^2 is a hydrogen or a lower alkyl, or a salt thereof. The pyrazolopyridine compound (I) and a salt thereof of the present invention are adenosine antagonists and are useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure, and the like.

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DESCRIPTION

PYRAZOLOPYRIDINE AS ADENOSINE ANTAGONISTS

TECHNICAL FIELD

The present invention relates to a novel pyrazolopyridine compound and a salt thereof, which are useful as medicaments.

BACKGROUND ART

Some pyrazolopyridine compounds to be useful as psychostimulant, remedy for renal failure, or the like are known (e.g. EP-0299209, EP-0379979, etc.).

DISCLOSURE OF INVENTION

The present invention relates to a novel pyrazolopyridine compound and a pharmaceutically acceptable salt thereof, which are useful as medicaments; processes for the preparation of said pyrazolopyridine compound and a salt thereof; a pharmaceutical composition comprising, as an active ingredient, said pyrazolopyridine compound or a pharmaceutically acceptable salt thereof; a use of said pyrazolopyridine compound or a pharmaceutically acceptable salt thereof as a medicament; and a method for using said pyrazolopyridine compound or a pharmaceutically acceptable salt thereof for therapeutic purposes, which comprises administering said pyrazolopyridine compound or a pharmaceutically acceptable salt thereof to a human being or an animal.

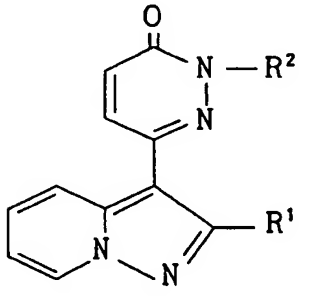
The pyrazolopyridine compound and a salt thereof are adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and possess various pharmacological actions such as anticatalepsy action, cognitive enhancing action, analgesic action, locomotor action, antidepressant action, diuretic action, cardioprotective action, cardiotonic action, vasodilating action (e.g. cerebral vasodilating action, etc.), the action of increasing the renal blood flow, renal protective action, improvement action of renal function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin

release, the action of increasing the production of erythropoietin, inhibiting action of platelet aggregation, or the like.

They are useful as cognitive enhancer, antianxiety drug, antidementia drug, psychostimulant, analgesic, cardioprotective agent, antidepressant, ameliorants of cerebral circulation, tranquilizer, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal failure (renal insufficiency), drug for renal toxicity, renal protective agent, drug for improvement of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilator, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppressive action of adenosine, antidiabetic agent, drug for ulcer, drug for pancreatitis, drug for Meniere's syndrome, drug for anemia; drug for thrombosis, drug for myocardial infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, drug for angina pectoris, or the like; and useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure; hypertension (e.g. essential hypertension, nephrogenous hypertension, etc.);
circulatory insufficiency (acute circulatory insufficiency) caused by, for example, ischemia/reperfusion injury (e.g. myocardial ischemia/reperfusion injury, cerebral ischemia/reperfusion injury, peripheral ischemia/reperfusion injury, etc.), shock (e.g. endotoxin shock, hemorrhagic shock, etc.), surgical procedure, or the like;
post-resuscitation asystole;
bradyarrhythmia;
electro-mechanical dissociation;
hemodynamic collapse;

SIRS (systemic inflammatory response syndrome);
multiple organ failure;
renal failure (renal insufficiency) (e.g. acute renal failure, etc.),
renal toxicity [e.g. renal toxicity induced by a drug such as cisplatins, gentamicin, FR-900506 (disclosed in EP-0184162), cyclosporin (e.g. cyclosporin A) or the like; glycerol, etc.],
nephrosis, nephritis, edema (e.g. cardiac edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, carcinomatous ascites, gestational edema, etc.);
obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer such as peptic ulcer (e.g. gastric ulcer, duodenal ulcer, etc.), pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus (e.g. mechanical ileus, adynamic ileus, etc.); and myocardial infarction, thrombosis (e.g. arterial thrombosis, cerebral thrombosis, etc.), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, or the like.

The novel pyrazolopyridine compound of the present invention can be shown by the following formula (I).



(I)

wherein

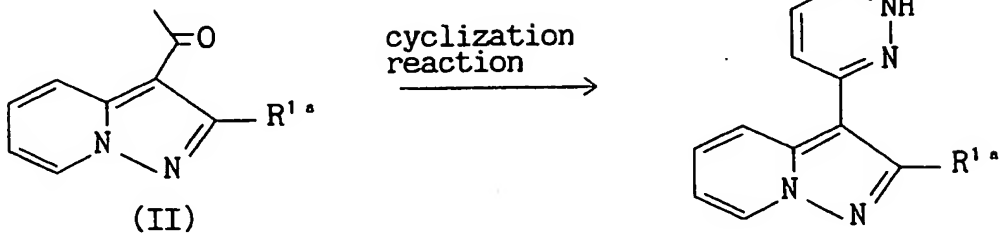
R^1 is a phenyl having one or two substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, hydroxy, lower alkoxy and ar(lower)alkoxy; and

R^2 is a hydrogen or a lower alkyl,

or a salt thereof.

The object compound (I) and a salt thereof of the present invention can be prepared by the following processes.

Process 1



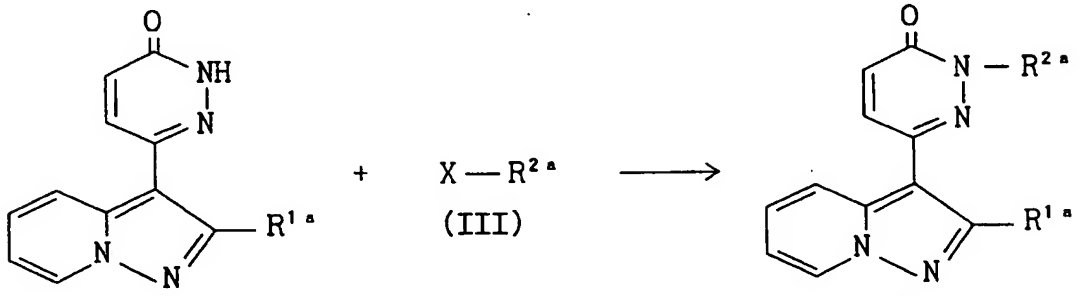
(II)

or a salt thereof

(Ia)

or a salt thereof

Process 2



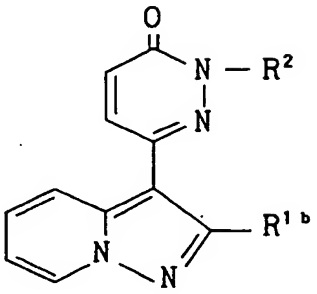
(Ia)

or a salt thereof

(Ib)

or a salt thereof

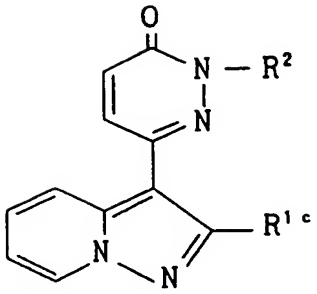
Process 3



(Ic)

or a salt thereof

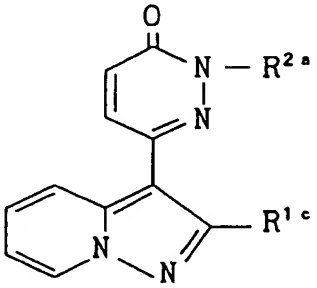
elinimation reaction of alkyl group



(Id)

or a salt thereof

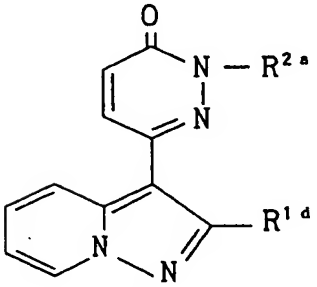
Process 4



(Ie)

or a salt thereof

+ $X-R^3$ (IV)



(If)

or a salt thereof

wherein

R^{1a} is a phenyl having one or two substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, lower alkoxy and ar(lower)alkoxy;

R^{1b} is a phenyl having one or two lower alkoxy and optionally having one or two substituent(s) selected from the group consisting of halogen, lower alkyl and halo(lower)alkyl;

R^{1c} is a phenyl having one or two hydroxy and optionally having one or two substituent(s) selected from the group consisting of halogen, lower alkyl and halo(lower)alkyl;

R^{1d} is a phenyl having one or two substituent(s) selected from the group consisting of lower alkoxy and ar(lower)alkoxy and optionally

having one or two substituent(s) selected from the group consisting of halogen, lower alkyl and halo(lower)alkyl;

R^2 is as defined above;

R^{2a} is a lower alkyl;

R^3 is a lower alkyl or an ar(lower)alkyl; and

X is a leaving group.

In addition to the processes as mentioned above, the object compound (I) and a salt thereof can be prepared, for example, according to the procedures as illustrated in Examples in the present specification or in a manner similar thereto.

The starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto.

The object compound (I) and a salt thereof can be prepared according to the methods as shown in Preparations or Examples, or in a manner similar thereto.

It is to be noted that the object compound (I) may include the geometrical isomer(s) due to the double bond(s) and/or the stereo isomer(s) due to the asymmetric carbon atom(s). In this regard, the isomer(s) can be converted to different isomer(s) according to a conventional method in this field of the art.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

Suitable salts of the object compound (I) are conventional pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylene-diamine salt, etc.), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate,

methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

Suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof and which appear in the above and following description in the present specification are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "halogen" may include fluoro, chloro, bromo and iodo.

Suitable "lower alkyl" may include straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl or the like, in which the preferred one may be (C_1-C_4) alkyl and the more preferred one may be methyl.

Suitable "halo(lower)alkyl" may include straight or branched ones such as fluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 4-fluorobutyl, 5-fluoropentyl, 6-fluorohexyl, chloromethyl, 1-chloroethyl, 2-chloroethyl, 1-chloropropyl, 2-chloropropyl, 3-chloropropyl, 4-chlorobutyl, 5-chloropentyl, 6-chlorohexyl, bromomethyl, 1-bromoethyl, 2-bromoethyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 4-bromobutyl, 5-bromopentyl, 6-bromohexyl, iodomethyl, 1-iodoethyl, 2-iodoethyl, 1-iodopropyl, 2-iodopropyl, 3-iodopropyl, 4-iodobutyl, 5-iodopentyl, 6-iodohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, trichloromethyl, 2,2,2-chloroethyl tribromomethyl, triiodomethyl or the like, in which the preferred one may be (C_1-C_4) alkyl.

Suitable "lower alkoxy" may include straight or branched ones such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which the preferred one may be (C_1-C_4) alkyl and the more preferred one may be methoxy.

Suitable "ar(lower)alkyl" may include phenyl(lower)alkyl (e.g.

benzyl, phenethyl, etc.), diphenyl(lower)alkyl (e.g. benzhydryl, etc.) or triphenyl(lower)alkyl (e.g. trityl, etc.) and the like, in which the preferred one may be phenyl(lower)alkyl, and the more preferred one may be phenyl (C_1-C_4) alkyl.

Suitable "leaving group" may include halogen as mentioned above, hydroxy, acyloxy such as alkanoyloxy (e.g. acetoxy, propionyloxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.), and the like.

The processes for preparing the object pyrazolopyridine compound (I) are explained in detail in the following.

Process 1

The compound (Ia) and a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to cyclization reaction.

Suitable salt of the compound (Ia) and (II) can be referred to the ones as exemplified for the compound (I).

The cyclization reaction of this process can be carried out, for example, by reacting the compound (II) or a salt thereof with glyoxylic acid or its reactive derivertive or a salt and hydrazine or a salt thereof.

Suitable salt of glyoxylic acid can be referred to a salt with a base as exemplified for the compound (I).

Suitable salt of hydrazine can be referred to a salt with a base as exemplified for the compound (I).

Suitable reactive derivertive of glyoxylic acid may be the ones conventionally used in this field of the art such as an activated ester thereof.

The reaction can be carried out in the presence or absence of a solvent.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 2

The compound (Ib) and a salt thereof can be prepared by reacting the compound (Ia) or a salt thereof with a compound of the formula $X-R^{2a}$ (III).

Suitable salt of the compound (Ia) and (Ib) can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may be also used in a mixture with water.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal alkoxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride, organic base such as benzyltrimethylammonium hydroxide, trimethylamine, and the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

Process 3

The compound (Id) and a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to elimination reaction of alkyl group.

Suitable salt of the compound (Ic) and (Id) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional

method such as hydrolysis.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), hydroxide or carbonate or bicarbonate thereof, trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]octane, 1,8-diazabicyclo[5,4,0]undec-7-ene, or the like.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.), and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.). The elimination using Lewis acid such as trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid, etc.) or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran or any other organic solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent.

The reaction of this process can be also carried out according to a conventional reduction method employed in this field of the art (e.g. chemical reduction, catalytic reduction, etc.).

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 4

The compound (If) and a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with a compound of the formula $X-R^3$ (IV).

Suitable salt of the compound (Ie) and (If) can be referred to the ones as exemplified for the compound (I).

The reaction of this process can be carried out in the manner similar to that of Process 2.

The object compound (I) of the present invention is an adenosine antagonist and possesses the various pharmacological actions as stated before.

In order to show the usefulness of the compound (I) of the present invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test : Adenosine antagonistic activity

[I] Test Method

The adenosine antagonistic activity [Ki(nM)] of the test compound was examined by radioligand binding techniques using 8-cyclopentyl-1,3-dipropylxanthine, [dipropyl-2,3-^{3}H(N)] ([^{3}H]DPCPX, 4.5nM) for human A_1 receptor and [^{3}H]CGS 21680 (20nM) for human A_{2a} receptor.

[II] Test Compound

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-methoxyphenyl)-pyrazolo[1,5-a]pyridine (Example 8)

2-(3-Chlorophenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo-[1,5-a]pyridine (Example 19)

2-(3-Chlorophenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (Example 20)

[III] Test Result

Table 1

Test compound (Example No.)	Adenosine Receptor Binding (Human) (Ki:nM)	
	A_1	A_{2a}
8	1	1.7
19	0.66	15
20	0.92	17

The pyrazolopyridine compound (I) and a salt thereof of this invention are usuful as adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and for the prevention and/or the treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack , angina pectoris, and the like.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the pyrazolopyridine compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. In addition, auxiliary, stabilizing agents, thickening agents, coloring agents and perfumes may be used where necessary. The pyrazolopyridine compound (I) or a

pharmaceutically acceptable salt thereof is included in a pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous, intramuscular, pulmonary or oral administration, or insufflation. While the dosage of therapeutically effective amount of the pyrazolopyridine compound (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the pyrazolopyridine compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.1 - 100 mg of the pyrazolopyridine compound (I) per kg weight of a human being or an animal, and in case of oral administration, a daily dose of 0.5 - 100 mg of the pyrazolo-pyridine compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the aforesaid diseases.

The following Preparation and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a mixture of 2-iodoanisole (5 g), dichlorobis(triphenyl-phosphine)palladium(II) (150 mg) and copper(I) iodide (41 mg) in a mixture of N,N-dimethylformamide (50 ml) and triethylamine (20 ml) was added dropwise (trimethylsilyl)acetylene (3.9 ml) at ambient temperature under nitrogen atmosphere, and the mixture was stirred for 2 hours. The solvent was removed under reduced pressure to give a residue, which was partitioned between a mixture of n-hexane and ethyl acetate (1:1) and water. The organic layer was separated, washed successively with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl

acetate=10/1) to give (2-methoxyphenylethynyl)trimethylsilane (4.2 g) as an oil.

^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 3.87 (s, 3H), 6.82-6.92 (m, 2H), 7.23-7.32 (m, 1H), 7.41-7.46 (m, 1H).

Preparation 2

A mixture of (2-methoxyphenylethynyl)trimethylsilane (4.15 g) and a saturated solution of potassium carbonate in methanol (50 ml) was stirred for 30 minutes at ambient temperature. The solvent was removed under reduced pressure to give a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=10/1) to give 1-ethynyl-2-methoxybenzene (2.17 g) as an oil.

^{1}H NMR ($CDCl_3$) δ 3.31 (s, 1H), 3.89 (s, 3H), 6.86-6.95 (m, 2H), 7.25-7.36 (m, 1H), 7.43-7.49 (m, 1H).

Preparation 3

To a solution of ethylmagnesium bromide (0.92 M in THF, 19 ml) in tetrahydrofuran (10 ml) was added dropwise 1-ethynyl-2-methoxybenzene (2.15 g) at ambient temperature under nitrogen atmosphere. After stirred for 1 hour, the reaction mixture was added dropwise to a solution of acetic anhydride (3.3 ml) in tetrahydrofuran (10 ml) at -2 to 5 ℃ under nitrogen atmosphere. After stirred for 1 hour at 5℃, to the reaction mixture was added carefully methanol (15 ml), and the mixture was stirred overnight at ambient temperature. Insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure to give a residue, which was partitioned between ethyl acetate and water. The organic layer was washed successively with water, saturated sodium hydrogencarbonate in water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=10/1, 4/1) to give 4-(2-

methoxyphenyl)-3-butyn-2-one (2.47 g) as a solid.
^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.87 (s, 3H), 6.89-6.99 (m, 2H), 7.37-7.53 (m, 2H);
(+)-APCI/MS m/z 175 $(M+H)^+$.

Preparation 4

To a mixture of 1-aminopyridinium iodide (4.4 g), benzyltriethylammonium chloride (295 mg) and sodium hydroxide (1.6 g) in water (10 ml) and dichloromethane (10 ml) was added dropwise a solution of 4-(2-methoxyphenyl)-3-butyn-2-one (2.3 g) in dichloromethane (10 ml) at 4 to 10 ℃, and the mixture was stirred vigorously for 2 hours. The reaction mixture was partitioned between dichloromethane and water. The organic layer was separated, washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=2/1 and dichloromethane/ethyl acetate=2/1). Recrystallization from a mixture of n-hexane and ethyl acetate afforded 3-acetyl-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (2.46 g) as a solid.
mp 149.0-150.5℃ (n-hexane-EtOAc);
FT-IR (KBr) 1643.1, 1506.1, 1469.5, 1434.8, 1415.5 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 3.80 (s, 3H), 6.99-7.15 (m, 3H), 7.40-7.53 (m, 3H), 8.43-8.55 (m, 2H);
(+)-APCI/MS m/z 267 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52.
Found: C, 72.00; H, 5.26; N, 10.43.

Example 1

A mixture of 3-acetyl-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (2.4 g) and glyoxylic acid monohydrate (2.5 g) in 1,2-dimethoxyethane (13 ml) was refluxed for 46 hours with stirring. Evaporation of the solvent gave a residue, which was dissolved in 28 % aqueous ammonia solution (60 ml) and to which was added hydrazine monohydrate (4.4 ml). After refluxed for 8 hours with stirring, the reaction mixture was cooled to ambient temperature and insoluble solid was collected

by filtration. The solid was washed with water, and recrystallized from ethanol to give 2-(2-methoxyphenyl)-3-(3-oxo-2,3-dihydro-pyridazin-6-yl)pyrazolo[1,5-a]pyridine (2.08 g) as a pale yellow solid.

mp over 265℃ (EtOH);

FT-IR (KBr) 1672.0, 1635.3, 1589.1, 1523.5, 1473.3, 1436.7 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.64 (s, 3H), 6.77 (d, 1H, J = 9.9 Hz), 6.85-7.00 (m, 2H), 7.06-7.16 (m, 2H), 7.31 (d, 1H, J = 6.8 Hz), 7.44-7.51 (m, 1H), 7.59 (d, 1H, J = 7.4 Hz), 8.16 (d, 1H, J = 8.9Hz), 8.53 (d, 1H, J = 6.9 Hz), 11.27 (s, 1H);

(+)-APCI/MS m/z 319 $(H+H)^+$;

Anal. Calcd for $C_{18}H_{14}N_4O_2 \cdot 0.25\ H_2O$: C, 66.97; H, 4.53; N, 17.35.
Found: C, 67.04; H, 4.35; N, 17.45.

Example 2

To a mixture of 2-(2-methoxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (1.5 g) and sodium hydride (60 % dispersion in mineral oil, 265 mg) in N,N-dimethylformamide (20 ml) was added methyl iodide (380 μl) and the mixture was stirred for 1 hour at ambient temperature under nitrogen atmosphere. To the reaction mixture was added water (100 ml) and insoluble solid was collected by filtration, which was recrystallized from ethanol to give 2-(2-methoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (2.08 g) as a pale yellow solid.

mp 211.5-212.5℃ (EtOH);

FT-IR (KBr) 3251.4, 3170.4, 1666.2, 1629.6, 1587.1, 1527.3, 1498.4, 1473.3, 1405.9 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.89 (s, 3H), 6.72 (d, 1H, J = 9.7 Hz), 6.88-7.15 (m, 4H), 7.32 (dt, 1H, J = 5.6, 1.1 Hz), 7.42-7.50 (m, 1H), 7.56 (dd, 1H, J = 7.5, 1.7 Hz), 8.15 (dt, 1H, J = 9.0, 1.2 Hz), 8.25 (dt, 1H, J = 6.9, 1.0 Hz);

(+)-APCI/MS m/z 333 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{16}N_4O_2 \cdot 0.25\ H_2O$: C, 67.75; H, 4.94; N, 16.63.
Found: C, 67.53; H, 4.47; N, 16.57.

Example 3

A stirred mixture of 2-(2-methoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (590 mg) in 48 % aqueous hydrobromic acid (10 ml) was refluxed for 8 hours. The reaction mixture was cooled to ambient temperature, to which was added 28 % aqueous ammonia solution (50 ml), and the mixture was stirred for 1 hour. Insoluble solid was collected by filtration and recrystallized from ethanol to give 2-(2-hydroxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (0.59 g) as a pale yellow solid.

mp 249.0-250.0℃ (EtOH);

FT-IR (KBr) 3158.8, 3079.8, 1658.5, 1579.4, 1531.2, 1502.3, 1448.3 cm^{-1};

^1H NHR (DMSO-d_6) δ 3.74 (s, 3H), 6.78-7.10 (m, 5H), 7.25-7.50 (m, 3H), 8.14 (d, 1H, J = 9.1 Hz), 8.78 (d, 1H, J = 6.9 Hz), 9.65 (s, 1H);

(+)-APCI/MS m/z 319 $(M+H)^+$;

Anal. Calcd for $C_{18}H_{14}N_4O_2 \cdot 0.75\ H_2O$: C, 65.15; H, 4.71; N, 16.88.
Found: C, 64.93; H, 4.28; N, 16.88.

Example 4

A stirred mixture of 2-(2-methoxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (600 mg) in 48 % aqueous hydrobromic acid (10 ml) was refluxed for 3 hours. The reaction mixture was cooled to ambient temperature, to which was added 28 % aqueous ammonia solution (50 ml), and the mixture was stirred for 1 hour. Insoluble solid was collected by filtration and recrystallized from ethanol to give 2-(2-hydroxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (424 mg) as a pale yellow solid.

mp over 265℃ (EtOH);

FT-IR (KBr) 3251.4, 3170.4, 1666.2, 1633.4, 1585.2, 1529.3, 1481.1, 1452.1, 1417.4 cm $^{-1}$;

^{1}H NMR (DMSO-d_6) δ 6.77 (d, 1H, J = 9.9 Hz), 6.90-7.11 (m, 4H), 7.25-7.46 (m, 3H), 8.00 (d, 1H, J = 8.9 Hz), 8.77 (d, 1H, J = 6.9 Hz), 9.64 (br-s, 1H), 12.95 (br-s, 1H);

(+)-APCI/MS m/z 305 $(M+H)^+$;

Anal. Calcd for $C_{17}H_{12}N_4O_2 \cdot 0.25\ H_2O$: C, 66.12; H, 4.07; N, 18.14.
Found: C, 66.21; H, 3.94; N, 18.17.

Preparation 5

(3-Methoxyphenylethynyl)trimethylsilane (20.05 g, 98.1 %) was prepared by a procedure similar to that of Preparation 1.

^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 3.79 (s, 3H), 6.83-6.90 (m, 1H), 6.97-7.10 (m, 2H), 7.16-7.25 (m, 1H).

Preparation 6

1-Ethynyl-3-methoxybenzene (11.46 g, 88.8 %) was prepared by a procedure similar to that of Preparation 2.

^{1}H NMR ($CDCl_3$) δ 3.43 (s, 1H), 3.80 (s, 3H), 6.87-6.95 (m, 1H), 7.00-7.12 (m, 2H), 7.18-7.32 (m, 1H).

Preparation 7

4-(3-Methoxyphenyl)-3-butyn-2-one (13.44 g, 92.8 %) was prepared by a procedure similar to that of Preparation 3.

^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.79 (s, 3H), 6.97-7.04 (m, 1H), 7.07-7.20 (m, 2H), 7.25-7.35 (m, 1H);

(+)-APCI/MS m/z 175 $(M+H)^+$.

Preparation 8

3-Acetyl-2-(3-methoxyphenyl)pyrazolo[1,5-a]pyridine (16.11 g, 81.1 %) was prepared by a procedure similar to that of Preparation 4.

mp 149.0-150.5℃ (n-hexane-EtOAc);

FT-IR (KBr) 1639.2, 1596.8, 1502.3, 1461.8, 1421.3 cm $^{-1}$;

^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 3.87 (s, 3H), 6.01-7.18 (m, 4H), 7.37-7.53 (m, 2H), 8.41-8.55 (m, 2H);

(+)-APCI/MS m/z 267 $(H+H)^+$;

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52.
Found: C, 72.25; H, 5.22; N, 10.48.

Example 5

2-(3-Methoxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo-[1,5-a]pyridine (11.7 g, 61.2 %) was prepared by a procedure similar to that of Example 1.

mp 193.5-195.0℃ (EtOH);

FT-IR (KBr) 1672.0, 1635.3, 1589.1, 1523.5, 1471.4, 1436.7 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.84 (d, 1H, J = 9.8 Hz), 6.88-7.04 (m, 2H), 7.10-7.19 (m, 3H), 7.24-7.42 (m, 2H), 8.07 (d, 1H, J = 8.9 Hz), 8.53 (d, 1H, J = 7.0 Hz), 12.38 (s, 1H);

(+)-APCI/MS m/z 319 $(M+H)^+$;

Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60.
Found: C, 67.59; H, 4.26; N, 17.53.

Example 6

2-(3-Methoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (1.03 g, 66 %) was prepared by a procedure similar to that of Example 2.

mp 150.5-151.5℃ (EtOH);

FT-IR (KBr) 1672.0, 1591.0, 1527.3, 1465.6, 1407.8 cm^{-1};

^1H NMR (DMSO-d_6) δ 3.76 (s, 3H), 3.78 (s, 3H), 6.87 (d, 1H, J = 9.6 Hz), 7.01-7.16 (m, 5H), 7.35-7.47 (m, 2H), 8.00 (dd, 1H, J = 7.8, 1.1 Hz), 8.81 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 333 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{16}N_4O_2 \cdot 0.25\ H_2O$: C, 67.75; H, 4.94; N, 16.63.
Found: C, 67.53; H, 4.74; N, 16.57.

Example 7

2-(3-Hydroxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (482 mg, 84.1 %) was prepared by a procedure similar to that of Example 3.

mp over 260℃ (EtOH);

FT-IR (KBr) 3236.0, 1666.2, 1587.1, 1529.3, 1496.5, 1452.1,

1405.9 cm $^{-1}$;

^{1}H NHR (DMSO-d_6) δ 3.76 (s, 3H), 6.82-6.90 (m, 2H),
6.99-7.11 (m, 4H), 7.23-7.32 (m, 1H), 7.37-7.47 (m, 1H),
7:98 (d, 1H, J = 8.9 Hz), 8.79 (d, 1H, J = 6.9 Hz), 9.58 (s, 1H);

(+)-APCI/MS m/z 319 $(M+H)^+$;

Anal. Calcd for $C_{18}H_{14}N_4O_2 \cdot 0.75\ H_2O$: C, 65.15; H, 4.71; N, 16.88.
Found: C, 64.93; H, 4.28; N, 16.80.

Example 8

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-methoxyphenyl)pyrazolo[1,5-a]pyridine (610 mg, 67.7 %) was prepared by a procedure similar to that of Example 2.

mp 120.8-121.4℃ (EtOH);

FT-IR (KBr) 1600.4, 1589.1, 1531.2, 1473.3, 1427.1 cm^{-1};

^{1}H NMR (DMSO-d_6) δ 1.33 (d, 6H, J = 6.6 Hz), 3.78 (s, 3H),
5.23 (sep, 1H, J = 6.6 Hz), 6.88 (d, 1H, J = 9.6 Hz),
7.01-7.08 (m, 5H), 7.35-7.50 (m, 2H), 7.92 (d, 1H, J = 8.9 Hz),
8.83 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 361 $(M+H)^+$;

Anal. Calcd for $C_{21}H_{20}N_4O_2 \cdot 0.125\ H_2O$: C, 69.36; H, 5.61; N, 15.41.
Found: C, 69.38; H, 5.48; N, 15.41.

Example 9

2-(3-Hydroxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo-[1,5-a]pyridine (530 mg, 92.7 %) was prepared by a procedure similar to that of Example 4.

mp over 260℃ (EtOH);

FT-IR (KBr) 3085.5, 3045.9, 1650.8, 1577.5, 1531.2, 1471.4,
1417.4 cm $^{-1}$;

^{1}H NMR (DMSO-d_6) (partial) δ 6.81-6.86 (m, 1H),
6.83 (d, 1H, J = 9.8 Hz), 6.99-7.09 (m, 3H), 7.12 (d, 1H, J = 9.8 Hz)
,7.22-7.29 (m, 1H), 7.30-7.45 (m, 1H), 7.84 (d, 1H, J = 8.9 Hz),
8.78 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 305 $(M+H)^+$;

Anal. Calcd for $C_{17}H_{12}N_4O_2 \cdot 0.125\ H_2O$: C, 66.61; H, 4.03; N, 18.28.
Found: C, 66.57; H, 3.96; N, 18.32.

Preparation 9

(4-Methoxyphenylethynyl)trimethylsilane (19 g, 109 %) was prepared by a procedure similar to that of Preparation 1.
^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 3.81 (s, 3H), 6.78-6.86 (m, 2H), 7.37-7.45 (m, 2H).

Preparation 10

1-Ethynyl-4-methoxybenzene (10.85 g, 88.3 %) was prepared by a procedure similar to that of Preparation 2.
^{1}H NMR ($CDCl_3$) δ 2.99 (s, 1H), 3.80 (s, 3H), 6.79-6.88 (m, 2H), 7.39-7.47 (m, 2H).

Preparation 11

4-(4-Methoxyphenyl)-3-butyn-2-one (12.96 g, 91.3 %) was prepared by a procedure similar to that of Preparation 3.
^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.84 (s, 3H), 6.87-6.94 (m, 2H), 7.49-7.57 (m, 2H);
(+)-APCI/MS m/z 175 $(M+H)^+$.

Preparation 12

3-Acetyl-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyridine (17.1 g, 86.8 %) was prepared by a procedure similar to that of Preparation 4.
mp 172.8-174.2℃ (EtOAc);
FT-IR (KBr) 1631.5, 1525.2, 1498.4, 1427.1 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.89 (s, 3H), 6.97-7.07 (m, 3H), 7.43-7.56 (m, 3H), 8.42 (d, 1H, J = 8.9 Hz), 8.51 (d, 1H, J = 6.9 Hz);
(+)-APCI/MS m/z 267 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot 0.25\ H_2O$: C, 70.96; H, 5.40; N, 10.34.
Found: C, 70.90; H, 5.19; N, 10.28.

Example 10

2-(4-Methoxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo-[1,5-a]pyridine (1.43 g, 45 %) was prepared by a procedure similar to that of Example 1.

mp 258.0-261.0℃ (EtOH);
FT-IR (KBr) 1673.9, 1585.2, 1523.5, 1468.5, 1413.6 cm $^{-1}$;
^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.82 (d, 1H, J = 9.9 Hz),
6.86-7.02 (m, 3H), 7.12 (d, 1H, J = 9.9 Hz), 7.24-7.33 (m, 1H),
7.54 (d, 1H, J = 8.5 Hz), 7.92 (d, 1H, J = 8.9 Hz),
8.22 (d, 1H, J = 6.9 Hz), 11.32 (s, 1H);
(+)-APCI/MS m/z 319 $(M+H)^+$;
Anal. Calcd for $C_{18}H_{14}N_4O_2 \cdot 0.25\ H_2O$: C, 67.44; H, 4.48; N, 17.48.
Found: C, 67.51; H, 4.38; N, 17.53.

Example 11

2-(4-Methoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (832 mg, 53.3 %) was prepared by a procedure similar to that of Example 2.
mp 157.0-158.0℃ (EtOH);
FT-IR (KBr) 1666.2, 1592.9, 1527.3, 1496.5, 1467.6, 1411.6 cm $^{-1}$;
^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H), 3.82 (s, 3H),
6.87 (d, 1H, J = 9.6 Hz), 7.01-7.11 (m, 4H), 7.35-7.47 (m, 1H),
7.54 (d, 1H, J = 8.7 Hz), 7.97 (d, 1H, J = 8.9 Hz),
8.78 (d, 1H, J = 6.9 Hz);
(+)-APCI/MS m/z 333 $(M+H)^+$;
Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86.
Found: C, 68.74; H, 4.85; N, 16.89.

Example 12

2-(4-Hydroxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (381 mg, 79.9 %) was prepared by a procedure similar to that of Example 3.
mp over 260℃ (EtOH);
FT-IR (KBr) 3344.0, 3101.0, 1650.8, 1618.0, 1577.5, 1531.2, 1500.3,
1469.5, 1419.4 cm $^{-1}$;
^{1}H NMR (DMSO-d_6) (partial) δ 3.76 (s, 3H), 6.83-6.89 (m, 3H),
6.99-7.11 (m, 2H), 7.35-7.45 (m, 3H), 7.96 (d, 1H, J = 8.9 Hz),
8.76 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 319 $(M+H)^+$;

Anal. Calcd for $C_{18}H_{14}N_4O_2 \cdot 1.25\ H_2O$: C, 63.43; H, 4.88; N, 16.44.
Found: C, 63.72; H, 4.83; N, 16.68.

Example 13

2-(4-Hydroxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo-[1,5-a]pyridine (463 mg, 80.1 %) was prepared by a procedure similar to that of Example 4.

mp over 260℃ (EtOH);

FT-IR (KBr) 3243.7, 1664.3, 1614.1, 1583.3, 1529.3, 1469.5, 1436.7, 1417.4 cm^{-1};

^1H NMR (DMSO-d_6) (partial) δ 6.79-6.88 (m, 3H),
7.01 (td, 1H, J = 6.9, 1.4 Hz), 7.11 (d, 1H, J = 9.8 Hz),
7.33-7.43 (m, 3H), 7.83 (d, 1H, J = 8.9 Hz),
8.75 (d, 1H, J = 6.9 Hz),;

(+)-APCI/MS m/z 305 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{16}N_4O_2 \cdot 0.2\ H_2O$: C, 66.31; H, 4.06; N, 18.20.
Found: C, 66.39; H, 3.93; N, 18.32.

Preparation 13

To a mixture of 3,4-dimethoxybromobenzene (4 ml), triphenylphosphine (73 mg), dichlorobis(triphenylphosphine)palladium(II) (150 mg) and copper(I) iodide (41 mg) in triethylamine (70 ml) was added dropwise (trimethylsilyl)acetylene (7.71 ml), and the mixture was refluxed overnight with stirring under nitrogen atmosphere. The solvent was removed under reduced pressure to give a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was dissolved in a saturated solution of potassium carbonate in methanol (100 ml), and the mixture was stirred for 3 hours at ambient temperature. The solvent was removed under reduced pressure to give a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine,

and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=10/1) to give 1-ethynyl-3,4-dimethoxybenzene (4.5 g) as an oil.

^{1}H NMR ($CDCl_3$) δ 3.00 (s, 1H), 3.85-3.89 (m, 6H), 6.71-6.83 (m, 1H), 6.97-7.13 (m, 2H)

Preparation 14

4-(3,4-Dimethoxyphenyl)-3-butyn-2-one (3.0 g, 53.6 %) was prepared by a procedure similar to that of Preparation 3.

^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 6.86 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 1.9 Hz), 7.21 (dd, 1H, J = 8.3, 1.9 Hz);

(+)-APCI/MS m/z 205 $(M+H)^+$.

Preparation 15

3-Acetyl-2-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyridine (4.0 g, 95.2 %) was prepared by a procedure similar to that of Preparation 4.

FT-IR (KBr) 1645.0, 1581.3, 1529.3, 1504.2, 1475.3, 1423.2, cm^{-1};

^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.97-7.17 (m, 4H), 7.44-7.53 (m, 2H), 8.42 (dt, 1H, J = 8.9, 1.2 Hz), 8.52 (dt, 1H, J = 6.9, 1.0 Hz);

(+)-APCI/MS m/z 297 $(M+H)^+$.

Example 14

2-(3,4-Dimethoxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (2.48 g, 53.4 %) was prepared by a procedure similar to that of Example 1.

mp 177.0-179.0℃ (EtOH);

FT-IR (KBr) 1681.6, 1589.1, 1529.3, 1479.1, 1429.0, 1402.0 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.95 (s, 3H), 6.84-6.97 (m, 3H), 7.11-7.31 (m, 3H), 8.05 (d, 1H, J = 8.9 Hz), 8.53 (d, 1H, J = 6.9 Hz), 12.90 (s, 1H);

(+)-APCI/MS m/z 349 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{16}N_4O_3 \cdot 0.7\ H_2O$: C, 63.22; H, 4.86; N, 15.52.

Found: C, 63.59; H, 4.69; N, 15.15.

Example 15

2-(3,4-Dimethoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (310 mg, 49.8 %) was prepared by a procedure similar to that of Example 2.

mp 160.0-161.0℃ (EtOH);

FT-IR (KBr) 1688.1, 1591.0, 1529.3, 1477.2, 1429.0 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.79 (d, 1H, J = 9.7 Hz), 6.87-6.95 (m, 2H), 7.05-7.20 (m, 3H), 7.30-7.35 (m, 1H), 8.00 (dt, 1H, J = 8.9, 1.2 Hz), 8.52 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 363 $(M+H)^+$;

Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46.

Found: C, 65.90; H, 4.94; N, 15.27.

Preparation 16

To a stirred mixture of 3-iodotoluene (4 ml), dichlorobis-(triphenylphosphine)palladium(II) (220 mg), copper(I) iodide (60 mg) and triphenylphosphine (81.7 mg) in triethylamine (60 ml) was added dropwise 3-butyn-2-ol (3.42 ml) at ambient temperature under nitrogen atmosphere. After the addition, the reaction mixture was refluxed under heating and stirred for 6 hours. The solvent was removed under reduced pressure to give a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=10/1, 2/1) to give 4-(3-methypheny1)-3-butyn-2-ol (4.88 g) as an oil.

^1H NMR ($CDCl_3$) δ 1.55 (d, 3H, J = 6.6 Hz), 2.32 (5, 3H), 4.75 (q, 1H, J = 6.6 Hz), 7.10-7.30 (m, 4H);

(+)-APCI/MS m/z 161 $(M+H)^+$.

Preparation 17

To a stirred solution of 4-(3-methyphenyl)-3-butyn-2-ol (4.8 g)

and triethylamine (13 ml) in a mixture of chloroform (25 ml) and dimethylsulfoxide (50 ml) was added sulphur trioxide-pyridine complex (6.2 g) by portions at 5℃ under nitrogen atmosphere. After 4 hours, the reaction mixture was partitioned between chloroform and water. The organic layer was separated, washed successively with 2 N aqueous hydrochloric acid and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=10/1 and 8/1) to give 4-(3-methyphenyl)-3-butyn-2-one (4.16 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.44 (s, 3H), 7.24-7.30 (m, 2H), 7.35-7.40 (m 2H).

Preparation 18

3-Acetyl-2-(3-methylphenyl)pyrazolo[1,5-a]pyridine (5.42 g, 82.1 %) was prepared by a procedure similar to that of Preparation 4.
mp 112.5-113.0℃, (h-hexane-EtOAc);
FT-IR (KBr) 1643.1, 1502.3, 1430.9, cm^{-1};
^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.44 (s, 3H),
7.20 (td, 1H, J = 6.9, 1.4 Hz), 7.27-7.53 (m, 5H),
8.17 (dt, 1H, J = 8.9, 1.1 Hz), 8.51 (dd, 1H, J = 6.9, 1.0 Hz);
(+)-APCI/MS m/z 251 $(M+H)^+$.

Example 16

2-(3-Methylphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (2.98 g, 49.3 %) was prepared by a procedure similar to that of Example 1.
mp 197.5-199.0℃ (EtOH);
FT-IR (KBr) 1677.8, 1587.1, 1521.6, 1465.6, 1432.9, 1405.9 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 6.80-7.00 (m, 2H),
7.12 (d, 1H, J = 9.8 Hz), 7.20-7.55 (m, 5H),
8.07 (d, 1H, J = 8.8 Hz), 8.53 (d, 1H, J = 6.9 Hz), 12.54 (s, 1H);
(+)-APCI/MS m/z 303 $(M+H)^+$;
Anal. Calcd for $C_{18}H_{14}N_4O \cdot 0.25\ H_2O$: C, 70.46; H, 4.76; N, 18.26.
Found: C, 70.76; H, 4.69; N, 18.31.

Example 17

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-methylphenyl)-pyrazolo[1,5-a]pyridine (470 mg, 75.1 %) was prepared by a procedure similar to that of Example 2.

mp 157.0-158.0℃ (EtOH);

FT-IR (KBr) 1658.5, 1585.2, 1527.3, 1471.4, 1402.0 cm^{-1};

^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.92 (s, 3H),
6.76 (d, 1H, J = 9.6 Hz),6.91 (td, 1H, J = 6.9, 1.4 Hz),
7.03 (d, 1H, J = 9.6 Hz), 7.25-7.40 (m, 4H), 7.47 (s, 1H),
8.02 (dt, 1H, J = 8.9, 1.1 Hz), 8.53 (dt, 1H, J = 6.9, 1.0 Hz);

(+)-APCI/MS m/z 317 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{16}N_4O \cdot 0.25\ H_2O$: C, 71.22; H, 5.19; N, 17.49.
Found: C, 71.42; H, 5.11; N, 17.49.

Example 18

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-methylphenyl)pyrazolo[1,5-a]pyridine (702 mg, 41.3 %) was prepared by a procedure similar to that of Example 2.

mp 147.0-147.5℃ (EtOH);

FT-IR (KBr) 1658.5, 1587.1, 1527.4, 1465.5, 1407.8 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.48 (d, 6H, J = 6.6 Hz), 2.40 (s, 3H),
5.44 (sep, 1H, J = 6.9, 1.4 Hz), 6.74 (d, 1H, J = 9.6 Hz),
6.91 (td, 1H, J = 6.9, 1.4 Hz), 7.02 (d, 1H, J = 9.6 Hz),
7.28-7.40 (m, 4H), 7.47 (s, 1H), 8.01 (dt, 1H, J = 8.9, 1.1 Hz),
8.53 (dd, 1H, J = 6.9, 1.0 Hz);

(+)-APCI/MS m/z 345 $(M+H)^+$;

Anal. Calcd for $C_{21}H_{20}N_4O_2 \cdot 0.25\ H_2O$: C, 67.75; H, 4.94; N, 16.63.
Found: C, 67.53; H, 4.47; N, 16.57.

Preparation 19

4-(3-Chlorophenyl)-3-butyn-2-ol (3.81 g, 65.2 %) was prepared by a procedure similar to that of Preparation 16.

^1H NMR ($CDCl_3$) δ 1.55 (d, 3H, J = 6.6 Hz),
4.75 (q, 1H, J = 6.6 Hz), 7.15-7.35 (m, 3H), 7.40-7.43 (m, 1H).

Preparation 20

4-(3-Chlorophenyl)-3-butyn-2-one (3.32 g, 88.5 %) was prepared by a procedure similar to that of Preparation 17.

^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 7.26-7.49 (m, 3H), 7.54-7.57 (m, 1H).

Preparation 21

3-Acetyl-2-(3-chlorophenyl)pyrazolo[1,5-a]pyridine (4.22 g, 84.4 %) was prepared by a procedure similar to that of Preparation 4.

mp 124.0-124.5℃ (n-hexane-EtOAc);

FT-IR (KBr) 1648.8, 1623.8, 1567.8, 1506.1, 1423.2 cm $^{-1}$;

^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 7.05 (td, 1H, J = 6.9, 1.4 Hz), 7.39-7.55 (m, 4H), 7.61-7.63 (m, 1H), 8.42 (dt, 1H, J = 8.9, 1.2 Hz), 8.52 (dt, 1H, J = 6.9, 1.0 Hz).

Example 19

2-(3-Chlorophenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (3.19 g, 66.9 %) was prepared by a procedure similar to that of Example 1.

mp 220.0-222.0℃ (EtOH);

FT-IR (KBr) 1685.5, 1587.1, 1523.5, 1467.6, 1403.9 cm $^{-1}$;

^{1}H NMR (DMSO-d_6) δ 6.87 (d, 1H, J = 8.8 Hz), 7.05-7.13 (m,1H), 7.21 (d, 1H, J = 9.8 Hz), 7.35-7.55 (m, 4H), 7.66 (s, 1H), 7.85 (d, 1H, J = 8.9 Hz), 8.82 (d, 1H, J = 6.9 Hz), 13.19 (s, 1H);

(+)-APCI/MS m/z 323 $(M+H)^+$;

Anal. Calcd for $C_{17}H_{11}ClN_4O$: C, 63.26; H, 3.44; N, 17.36.

Found: C, 62.84; H, 3.33; N, 17.24.

Example 20

2-(3-Chlorophenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (550 mg, 87.8 %) was prepared by a procedure similar to that of Example 2.

mp 158.0-159.0℃ (EtOH);

FT-IR (KBr) 1675.8, 1631.5, 1589.1, 1529.3, 1467.6, 1421.3, cm^{-1};

^{1}H NMR (DMSO-d_6) δ 3.33 (s, 3H), 6.90 (d, 1H, J = 9.6 Hz), 7.06-7.14 (m, 1H), 7.16 (d, 1H, J = 9.6 Hz), 7.40-7.59 (m, 4H),

7.69-7.71 (m, 1H), 7.99 (d, 1H, J = 8.9 Hz), 8.83 (d, 1H, J = 6.9 Hz);
(+)-APCI/MS m/z 337 $(M+H)^+$;
Anal. Calcd for $C_{18}H_{13}ClN_4O \cdot 0.25\ H_2O$: C, 63.35; H, 3.99; N, 16.42.
Found: C, 63.39; H, 3.75; N, 16.35.

Example 21

2-(3-Chlorophenyl)-3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (510 mg, 30.2 %) was prepared by a procedure similar to that of Example 2.
mp 142.0-142.5℃ (EtOH);
FT-IR (KBr) 1662.3, 1633.4, 1589.1, 1527.4, 1484.9, 1463.7, 1446.4, 1425.1, 1405.9 cm^{-1};
^1H NMR ($CDCl_3$) δ 1.46 (d, 6H, J = 6.6 Hz), 5.43 (sep, 1H, J = 6.6), 6.81 (d, 1H, J = 9.6 Hz), 6.93 (td, 1H, J = 6.9, 1.4 Hz), 7.04 (d, 1H, J = 9.6 Hz), 7.28-7.49 (m, 4H), 7.68 (d, 1H, J = 1.8 Hz), 7.96 (dt, 1H, J = 8.9, 1.1 Hz), 8.53 (dd, 1H, J = 6.9, 1.0 Hz);
(+)-APCI/MS m/z 365 $(M+H)^+$;
Anal. Calcd for $C_{20}H_{17}ClN_4O$: C, 65.84; H, 4.70; N, 15.36.
Found: C, 65.57; H, 4.64; N, 15.29.

Preparation 22

4-(3-Trifluoromethylphenyl)-3-butyn-2-ol (6.7 g, 100 %) was prepared by a procedure similar to that of Preparation 16.
^1H NMR ($CDCl_3$) δ 1.57 (d, 3H, J = 6.6 Hz), 4.77 (q, 1H, J = 6.6 Hz), 7.38-7.47 (m, 1H), 7.54-7.61 (m, 2H), 7.69 (s, 1H).

Preparation 23

4-(3-Trifluoromethylphenyl)-3-butyn-2-one (6.08 g, 93.1 %) was prepared by a procedure similar to that of Preparation 17.
^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 7.49-7.58 (m, 1H), 7.68-7.77 (m, 2H), 7.83 (s, 1H).

Preparation 24

3-Acetyl-2-(3-trifluoromethylphenyl)pyrazolo[1,5-a]pyridine (6.83

g, 79.3 %) was prepared by a procedure similar to that of Preparation 4.

mp 122.5-123.0℃ (n-hexane-EtOAc);

FT-IR (KBr) 1639.2, 1502.3, 1421.3 cm^{-1};

^1H NMR ($CDCl_3$) δ 2.18 (s, 3H), 7.07 (td, 1H, J = 6.9, 1.4 Hz), 7.47-7.68 (m, 2H), 7.75-7.85 (m, 1H), 7.91 (s, 1H), 8.42 (dt, 1H, J = 8.9, 1.2 Hz), 8.54 (dt, 1H, J = 6.9, 1.0 Hz);

(+)-APCI/MS m/z 305 $(M+H)^+$.

Example 22

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3-trifluoromethylphenyl)-pyrazolo[1,5-a]pyridine (4.35 g, 57.2 %) was prepared by a procedure similar to that of Example 1.

mp 201.5-203.0℃ (EtOH);

FT-IR (KBr) 1675.8, 1587.1, 1523.5, 1477.2, 1444.4, 1411.6 cm^{-1};

^1H NMR ($CDCl_3$) δ 6.85-7.00 (m, 2H), 7.08 (d, 1H, J = 9.8 Hz), 7.26-7.35 (m, 1H), 7.55-7.90 (m, 3H), 7.98 (s, 1H), 8.05 (d, 1H, J = 8.9 Hz), 8.54 (d, 1H, J = 6.9 Hz), 12.59 (s, 1H);

(+)-APCI/MS m/z 357 $(M+H)^+$;

Anal. Calcd for $C_{18}H_{11}F_3N_4O$: C, 60.68; H, 3.11; N, 15.72.

Found: C, 60.23; H, 2.96; N, 15.58.

Example 23

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-trifluoromethylphenyl)pyrazolo[1,5-a]pyridine (400 mg, 64.3 %) was prepared by a procedure similar to that of Example 2.

mp 153.0-154.0℃ (EtOH);

FT-IR (KBr) 1662.3, 1589.1, 1529.3, 1479.1, 1452.1, 1409.7 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.83 (d, 1H, J = 9.6 Hz), 6.91-7.00 (m, 1H), 7.02 (d, 1H, J = 9.6 Hz), 7.29-7.34 (m, 1H), 7.53-7.61 (m, 1H), 7.69-7.82 (m, 2H), 7.95-8.00 (m, 2H), 8.54 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 371 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{13}F_3N_4O \cdot 0.25\ H_2O$: C, 60.88; H, 3.63; N, 14.95.

Found: C, 60.56; H, 3.44; N, 14.79.

Example 24

To a mixture of 2-(3-hydroxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (520 mg) and sodium hydride (60 % dispersion in mineral oil, 85 mg) in N,N-dimethylformamide (20 ml) was added ethyl iodide (331 mg) and the mixture was stirred for 2 hours at ambient temperature under nitrogen atmosphere. To the reaction mixture was added water (100 ml) and insoluble solid was collected by filtration, which was recrystallized from ethanol to give 2-(3-ethoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (330 mg) as a pale yellow solid.

mp 113.8-115.0℃ (EtOH);

FT-IR (KBr) 1670.1, 1589.1, 1525.4, 1492.6, 1461.8 cm^{-1};

^1H NMR (DMSO-d_6) δ 1.33 (t, 3H, J = 6.9 Hz), 3.76 (s, 3H), 4.04 (q, 2H, J = 6.9 Hz), 6.87 (d, 1H, J = 9.6 Hz), 6.99-7.15 (m, 5H), 7.33-7.47 (m, 2H), 8.00 (d, 1H, J = 8.9 Hz), 8.81 (d, 1H, J = 6.9 Hz) ;

(+)-APCI/MS m/z 347 $(M+H)^+$;

Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17.

Found: C, 68.99; H, 5.18; N, 15.95.

Example 25

2-(3-Isopropoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (400 mg, 64.3 %) was prepared by a procedure similar to that of Example 24.

FT-IR (KBr) 1662.3, 1585.2, 1529.3, 1467.6 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.33 (d, 6H, J = 6.0 Hz), 3.92 (s, 3H), 4.57 (sep, 1H, J = 6.0 Hz), 6.78 (d, 1H, J = 9.6 Hz), 6.91-7.16 (m, 5H), 7.26-7.90 (m, 3H), 8.02 (dt, 1H, J = 8.9, 1.1 Hz), 8.53 (dd, 1H, J = 6.9, 1.0 Hz);

(+)-APCI/MS m/z 361 $(M+H)^+$.

Example 26

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-pentyloxyphenyl)pyrazolo[1,5-a]pyridine (120 mg, 98.4 %) was prepared by a procedure similar to that of Example 24.

FT-IR (KBr) 1664.3, 1587.1, 1529.3, 1400.1 cm^{-1};

^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.2 Hz), 1.29-1.90 (m, 6H), 3.92 (s, 3H), 3.98 (t, 1H, J = 6.5 Hz), 6.78 (d, 1H, J = 9.6 Hz), 6.91-7.18 (m, 2H), 7.27-7.38 (m, 2H), 8.03 (dt, 1H, J = 8.9, 1.1 Hz), 8.53 (dd, 1H, J = 7.0, 1.0 Hz);

(+)-APCI/MS m/z 389 $(M+H)^+$.

Example 27

2-(3-Benzyloxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (149.8 mg, 89.9 %) was prepared by a procedure similar to that of Example 24.

mp 169.5-171.0℃ (EtOH);

FT-IR (KBr) 1664.3, 1633.4, 1591.0, 1529.3, 1475.3, 1434.8 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 5.10 (s, 2H), 6.74 (d, 1H, J = 9.6 Hz), 6.91-7.19 (m, 4H), 7.26-7.42 (m, 8H), 8.02 (d, 1H, J = 8.9 Hz), 8.53 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 409 $(M+H)^+$;

Anal. Calcd for $C_{25}H_{20}N_4O_2$ 0.5 H_2O: C, 71.92; H, 5.07; N, 13.42.
Found: C, 72.28; H, 5.02; N, 12.96.

Preparation 25

A mixture of 2-methoxycinnamic acid (50 g) and sulfuric acid (2 ml) in methanol (650 ml) was refluxed for 12 hours with stirring. Evaporation of the solvent gave a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with brine, saturated sodium hydrogencarbonate in water and brine, and dried over magnesium sulfate. The organic solvent was removed under reduced pressure to give methyl 2-methoxycinnamate (55 g) as an oil.

^1H NMR (DMSO-d_6) δ 3.80 (s, 3H), 3.88 (s, 3H), 6.53 (d, 1H, J = 16.1 Hz), 6.91 (d, 1H, J = 8.3 Hz),

6.97 (d, 1H, J = 7.7 Hz), 7.35 (td, 1H, J = 7.6, 1.6 Hz),
7.50 (dd, 1H, J = 7.6, 1.6 Hz), 8.00 (d, 1H, J = 16.1 Hz);
(+)-APCI/MS m/z 193 $(M+H)^+$.

Preparation 26

To a solution of methyl 2-methoxycinnamate (55 g) in dichloromethane (500 ml) was added dropwise bromine (34 ml) and the mixture was stirred for 5.5 hours at ambient temperature. The reaction mixture was partitioned between dichloromethane and 5 % aqueous sodium thiosulfate solution. The organic layer was separated, washed with brine and dried over magnesium sulfate. The organic solvent was removed under reduced pressure to give methyl 3-(5-bromo-2-methoxyphenyl)-2,3-dibromopropionate (120 g) as a solid.
^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.91 (s, 3H),
5.08 (d, 1H, J = 11.8 Hz), 5.65 (d, 1H, J = 11.8 Hz),
6.80 (d, 1H, J = 9.3 Hz), 7.35-7.50 (m, 2H).

Preparation 27

A mixture of methyl 3-(5-bromo-2-methoxyphenyl)-2,3-dibromopropionate (100 g) and potassium hydroxide (59 g) in ethanol (95 %, 350 ml) was refluxed for 7 hours with stirring. Evaporation of the solvent gave a residue, which was dissolved in water and the pH was adjusted to 1 with 20 % aqueous sulfuric acid solution at 5℃. The resulting mixture was extracted with dichloromethane and dried over magnesium sulfate. The organic solvent was removed under reduced pressure to give a crude product, which was washed with a mixture of dichloromethane and n-hexane to give (5-bromo-2-methoxyphenyl)-propynoic acid (45.2 g) as a solid.
^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.49 (d, 1H, J = 8.9 Hz),
7.52 (dd, 1H,J = 8.9, 2.5 Hz), 7.65 (d, 1H, J = 2.5 Hz).

Preparation 28

Acetyl chloride (42.2 ml) was added dropwise to methanol (400 ml) at 0℃ under nitrogen atmosphere. After stirred for 15 minutes, to a mixture was added (5-bromo-2-methoxyphenyl)propynoic acid (42 g).

After addition, the reaction mixture was allowed to warm to ambient temperature and stirred overnight. Evaporation of the solvent gave a residue, which was partitioned between ethyl acetate and saturated sodium hydrogencarbonate in water. The organic layer was separated, washed successively with water and brine, and dried over magnesium sulfate. The organic solvent was removed under reduced pressure to give methyl (5-bromo-2-methoxyphenyl)propynoate (43.67 g) as a solid.
^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.88 (s, 3H),
6.47 (d, 1H, J = 8.9 Hz), 7.49 (dd, 1H, J = 8.9, 2.5 Hz),
7.62 (d, 1H, J = 2.5 Hz);
(+)-FAB/MS m/z 270, 272 $(M+H)^+$.

Preparation 29

To a mixture of 1-aminopyridinium iodide (39 g), benzyltriethylammonium chloride (2.7 g) and sodium hydroxide (19 g) in water (120 ml) and dichloromethane (300 ml) was added methyl (5-bromo-2-methoxyphenyl)propynoate (30 g) at 4 ℃ to 10℃ and the mixture was stirred vigorously for 2 hours. The reaction mixture was partitioned between dichloromethane and water. The organic layer was separated, washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was crystallized from ethyl acetate to give 2-(5-bromo-2-methoxyphenyl)-3-methoxycarbonylpyrazolo[1,5-a]pyridine (21 g) as a solid.
mp 193.0-194.0℃ ; FT-IR (KBr) 1718.3, 1633.4, 1513.8, 1477.2, 1438.6 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 3.77 (2 x s, 2 x 3H), 6.87 (d, 1H, J = 8.5 Hz),
6.96 (td, 1H, J = 6.9, 1.4 Hz), 7.37-7.56 (m, 3H),
8.17 (td, 1H, J = 8.9, 1.2 Hz), 8.52 (td, 1H, J = 6.9, 1.0 Hz);
Anal. Calcd for $C_{16}H_{13}BrN_2O_3$: C, 53.21; H, 3.63; N, 7.66.
Found: C, 53.06; H, 3.57; N, 7.65.

Preparation 30

A mixture of 2-(5-bromo-2-methoxyphenyl)-3-methoxycarbonylpyrazolo[1,5-a]pyridine (10 g), sodium acetate (4.5 g) and 10 %

palladium on carbon (50 % wet, 2 g) in N,N-dimethylformamide was stirred for 5 hours under hydrogen atmosphere at ambient temperature. Catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a residue, which was triturated with ethyl acetate. The resulting solid was collected by filtration. Recrystallization from ethanol afforded 3-methoxycarbonyl-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (6.61 g) as a solid.
mp 124.5-125.0℃;
FT-IR (KBr) 1708.6, 1631.5, 1610.3, 1517.7, 1473.3, 1442.5 cm^{-1};
^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.77 (s, 3H), 6.93-7.10 (m, 3H), 7.35-7.47 (m, 3H), 8.18 (dt, 1H, J = 8.9, 1.2 Hz), 8.52 (td, 1H, J = 8.9, 1.1 Hz);
(+)-APCI/MS M/Z 283 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92.
Found: C, 67.61; H, 4.84; N, 9.85.

Preparation 31

A mixture of 3-methoxycarbonyl-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (6.5 g) in 47 % aqueous hydrobromic acid (60 ml) was refluxed for 5.5 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give a residue, which was partitioned between chloroform and water. The organic layer was separated, washed successively with saturated sodium hydrogencarbonate in water and brine, dried over magnesium sulfate, and evaporated to give a residue. To a solution of the above residue in N,N-dimethylformamide (50 ml) was added successively sodium hydride (60 % dispersion in mineral oil, 1.1 g) and methyl iodide (1.72 ml) at 0℃ under nitrogen atmosphere and the mixture was stirred for 2 hours at that temperature. To the reaction mixture was added carefully water, and the mixture was concentrated under reduced pressure and partitioned between dichloromethane and water. The organic layer was separated, dried over magnesium sulfate, and purified by silica-gel column chromatography (dichloromethane/ethyl

acetate=9/1) to give 2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (5.12 g) as a solid.

mp 89.5-91.0℃ ;

FT-IR (KBr) 1629.6, 1600.6, 1610.3, 1581.3, 1515.8, 1477.2, 1413.6 cm $^{-1}$;

^{1}H NMR ($CDCl_3$) δ 3:95 (s, 3H), 6.71 (td, 1H, J = 6.9, 1.3 Hz), 7.00-7.11 (m, 4H), 7.30-7.40 (m, 1H), 7.51 (d, 1H, J = 8.9 Hz), 8.09 (dd, 1H, J = 7.6, 1.8 Hz), 8.48 (dd, 1H, J = 7.0, 1.0 Hz);

(+)-APCI/MS M/Z 225 $(M+H)^+$;

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49.

Found: C, 74.73; H, 5.48; N, 12.39.

Preparation 32

A stirred mixture of 2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (4.5 g) and acetic anhydride (12.5 ml) was heated at 130 ℃ and to which was added methanesulfonic acid (52 μl) under nitrogen atmosphere. After 2 hours, the reaction mixture was cooled to ambient temperature and methanol (4.05 ml) was added dropwise thereto. The reaction mixture was added to 9 % aqueous sodium hydroxide solution, stirred for 1 hour, extracted with dichloromethane, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (n-hexane/ethyl acetate=1/1 and dichloromethane/ethyl acetate=1/1) and recrystallized from a mixture of n-hexane and ethyl acetate to give 3-acetyl-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (5.23 g) as a solid.

mp 149.0-150.5℃ (n-hexane-EtOAc);

FT-IR (KBr) 1643.1, 1506.1, 1469.5, 1434.8, 1415.5 cm $^{-1}$;

^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 3.80 (s, 3H), 6.99-7.15 (m, 3H), 7.40-7.53 (m, 3H), 8.43-8.55 (m, 2H);

(+)-APCI/MS m/z 267 $(M+H)^+$;

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52.

Found: C, 72.00; H, 5.26; N, 10.43.

Preparation 33

Methyl 3-methoxycinnamate (54.0 g, 100.2 %) was prepared by a procedure similar to that of Preparation 25.

^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H), 3.82 (s, 3H), 6.42 (d, 1H, J = 16.0 Hz), 6.90-6.96 (m, 1H), 7.03-7.15 (m, 2H), 7.25-7.35 (m, 1H), 7.66 (d, 1H, J = 16.0 Hz).

Preparation 34

Methyl 2,3-dibromo-3-(3-methoxyphenyl)propionate (113 g, 114 %) was prepared by a procedure similar to that of Preparation 26.

^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 3.90 (s, 3H), 4.83 (d, 1H, J = 11.7 Hz), 5.30 (d, 1H, J = 11.7 Hz), 6.75-7.15 (m, 3H), 7.25-7.40 (m, 1H) .

Preparation 35

(3-Methoxyphenyl)propynoic acid (25.5 g, 47.7 %) was prepared by a procedure similar to that of Preparation 27.

^{1}H NMR ($CDCl_3$) (partial) δ 3.81 (s, 3H), 6.89 (d, 1H, J = 8.9 Hz), 6.92-7.35 (m, 3H);

(+)-FAB/MS m/z 177 $(M+H)^+$.

Preparation 36

Methyl (3-methoxyphenyl)propynoate (26.68 g, 96.9 %) was prepared by a procedure similar to that of Preparation 28.

^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.84 (s, 3H), 6.86 (d, 1H, J = 8.9 Hz), 6.97-7.35 (m, 3H);

(+)-APCI/MS m/z 191 $(M+H)^+$.

Preparation 37

3-Methoxycarbonyl-2-(3-methoxyphenyl)pyrazolo[1,5-a]pyridine (16.7 g, 41.9 %) was prepared by a procedure similar to that of Preparation 29.

mp 102.5-103.5℃ ;

^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.81 (s, 3H), 6.87 (d, 1H, J = 8.8 Hz), 6.95-7.05 (m, 2H), 7.35-7.57 (m, 3H), 8.22 (dt, 1H, J = 8.9, 1.1 Hz), 8.54 (dt, 1H, J = 6.9, 1.0 Hz);

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92.

Found: C, 67.76; H, 4.84; N, 9.81.

Preparation 38

2-(3-Methoxyphenyl)pyrazolo[1,5-a]pyridine (6.77 g, 73.5 %) was prepared by a procedure similar to that of Preparation 31.

mp 62.5-64.0℃ (n-hexane-EtOAc);

FT-IR (KBr) 1631.5, 1612.2, 1581.3, 1515.8, 1473.3 cm^{-1};

^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.72-6.79 (m, 2H), 6.90-7.00 (m, 1H), 7.05-7.15 (m, 1H), 7.30-7.40 (m, 1H), 7.45-7.60 (m, 3H), 8.47 (dt, 1H, J = 6.6, 0.7 Hz);

(+)-APCI/MS M/Z 225 $(M+H)^+$;

Anal. Calcd for $C_{14}H_{12}N_2O \cdot 0.125H_2O$: C, 74.24; H, 5.45; N, 12.37.

Found: C, 74.28; H, 5.48; N, 12.29.

Preparation 39

3-Acetyl-2-(3-methoxyphenyl)pyrazolo[1,5-a]pyridine (5.46 g, 80.7 %) was prepared by a procedure similar to that of Preparation 32.

mp 92.5-93.5℃ (n-hexane-EtOAc);

FT-IR (KBr) 1639.2, 1596.8, 1502.3, 1461.8, 1421.3 cm^{-1};

^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 3.87 (s, 3H), 6.01-7.18 (m, 4H), 7.37-7.53 (m, 2H), 8.41-8.55 (m, 2H);

(+)-APCI/MS m/z 267 $(M+H)^+$;

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52.

Found: C, 72.25; H, 5.22; N, 10.48.

Preparation 40

Methyl 4-methoxycinnamate (10.73 g, 99.4 %) was prepared by a procedure similar to that of Preparation 25.

^1H NMR (DMSO-d_6) δ 3.79 (s, 3H), 3.83 (s, 3H), 6.31 (d, 1H, J = 16.0 Hz), 6.90 (d, 2H, J = 8.7 Hz), 7.47 (d, 2H, J = 8.7 Hz), 7.65 (d, 1H, J = 16.0 Hz);

(+)-APCI/MS m/z 193 $(M+H)^+$.

Preparation 41

Methyl 2,3-dibromo-3-(4-methoxyphenyl)propionate (100.6 g, 103.7 %) was prepared by a procedure similar to that of Preparation 26.

^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.89 (s, 3H),
4.84 (d, 1H, J = 11.7 Hz), 5.36 (d, 1H, J = 11.7 Hz),
6.86-6.95 (m, 2H), 7.31-7.36 (m, 2H).

Preparation 42

(4-Methoxyphenyl)propynoic acid (21.4 g, 42.8 %) was prepared by a procedure similar to that of Preparation 27.

^{1}H NMR ($CDCl_3$) (partial) δ 3.85 (s, 3H), 6.90 (d, 2H, J = 8.6 Hz),
7.57 (d, 2H, J = 8.6 Hz);
(+)-FAB/MS m/z 177 $(M+H)^+$.

Preparation 43

Methyl (4-methoxyphenyl)propynoate (22.71 g, 98.3 %) was prepared by a procedure similar to that of Preparation 28.

^{1}H NMR ($CDCl_3$) δ 3.82 (2 x s, 2 x 3H), 6.85-6.95 (m, 2H),
7.45-7.60 (m, 2H);
(+)-APCI/MS m/z 191 $(M+H)^+$.

Preparation 44

3-Methoxycarbonyl-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyridine (6.41 g, 21.6 %) was prepared by a procedure similar to that of Preparation 29.

mp 166.0-167.0℃
FT-IR (KBr) 1700.9, 1612.2, 1533.1, 1506.1, 1473.3, 1423.2 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 3.87 (s, 3H), 6.90-7.05 (m, 3H),
7.35-7.45 (m, 2H), 7.73-7.81 (m, 2H), 8.19 (d, 1H, J = 8.9 Hz),
8.51 (d, 1H, J = 6.9 Hz);
(+)-APCI/MS M/Z 283 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{14}N_2O_3 \cdot 0.25\ H_2O$: C, 67.01; H, 5.01; N, 9.77.
Found: C, 66.67; H, 4.92; N, 9.68.

Preparation 45

2-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridine (330 mg, 6.5 %) was prepared by a procedure similar to that of Preparation 31.

mp 124.0-124.5℃ (n-hexane-EtOAc);
FT-IR (KBr) 1621.2, 1579.4, 1511.9, 1467.6, 1427.1 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.69-6.74 (m, 2H),
6.94-7.11 (m, 3H), 7.48 (dt, 1H, J = 8.9, 1.1 Hz), 7.85-7.31 (m, 2H),
8.45 (dd, 1H, J = 7.0, 1.0 Hz);
(+)-APCI/MS M/Z 225 $(M+H)^+$;
Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49.
Found: C, 75.14; H, 5.32; N, 12.32.

Preparation 46

2-(5-Bromo-2-methoxyphenyl)pyrazolo[1,5-a]pyridine (8.53 g, 93.4 %) was prepared by a procedure similar to that of Preparation 31.
mp 121.0-122.0℃ (n-hexane-EtOAc);
FT-IR (KBr) 1631.5, 1517.7, 1475.3, 1432.9 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.74 (td, 1H, J = 6.9, 1.4 Hz),
6.88 (d, 1H, J = 8.8 Hz), 7.00-7.12 (m, 2H),
7.42 (dd, 1H, J = 8.8, 2.6 Hz), 7.52 (dd, 1H, J = 8.9, 1.1 Hz),
8.25 (d, 1H, J = 2.6 Hz), 8.47 (dd, 1H, J = 7.0, 1.0 Hz);
(+)-APCI/MS M/Z 303, 305 $(M+H)^+$;
Anal. Calcd for $C_{14}H_{11}BrN_2O$: C, 55.47; H, 3.66; N, 9.24.
Found: C, 55.35; H, 3.75; N, 9.33.

Preparation 47

3-Acetyl-2-(5-bromo-2-methoxyphenyl)pyrazolo[1,5-a]pyridine (9.24 g, 95.7 %) was prepared by a procedure similar to that of Preparation 32.
mp 189.5-191.0℃ (n-hexane-CH_2Cl_2);
FT-IR (KBr) 1639.2, 1506.1, 1463.7, 1427.1 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.78 (s, 3H),
6.90 (d, 1H, J = 9.4 Hz), 7.01 (td, 1H, J = 6.9, 1.4 Hz),
7.43-7.61 (m, 3H), 8.44 (dd, 1H, J = 8.9, 1.2 Hz),
8.51 (d, 1H, J = 6.9, 1.0 Hz);
(+)-APCI/MS m/z 345, 347 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12.
Found: C, 55.56; H, 3.75; N, 8.03.

Example 28

2-(5-Bromo-2-methoxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (6.76 g, 65.3 %) was prepared by a procedure similar to that of Example 1.

mp over 265℃ (EtOH);

FT-IR (KBr) 1668.1, 1587.1, 1515.8, 1475.3, 1425.1 cm $^{-1}$;

^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 6.75-7.00 (m, 3H),
7.11 (d, 1H, J = 9.9 Hz), 7.60-7.40 (m, 1H), 7.50-7.80 (m, 2H),
8.13 (d, 1H, J = 9.0 Hz), 8.52 (d, 1H, J = 6.9 Hz), 11.26 (s, 1H);

(+)-APCI/MS m/z 337, 339 $(M+H)^+$;

Anal. Calcd for $C_{18}H_{13}BrN_2O_2$: C, 54.43; H, 3.30; N, 14.09.
Found: C, 54.08; H, 3.25; N, 14.09.

Example 29

2-(5-Bromo-2-methoxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (1.09 g, 52.9 %) was prepared by a procedure similar to that of Example 2.

mp 188.5-189.5℃ (EtOH);

FT-IR (KBr) 1666.2, 1589.1, 1527.3, 1490.7, 1473.3, 1421.3 cm $^{-1}$;

^{1}H NMR (DMSO-d_6) δ 3.53 (s, 3H), 3.73 (s, 3H),
6.84 (d, 1H, J = 9.7 Hz), 7.00-7.12 (m, 3H), 7.40-7.50 (m, 1H),
7.63-7.70 (m, 2H), 8.12 (d, 1H, J = 8.9 Hz), 8.79 (d, 1H, J = 6.9 Hz);

(+)-APCI/MS m/z 411, 413 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{15}BrN_4O_2 \cdot 0.125\ H_2O$: C, 55.19; H, 3.72; N, 13.55.
Found: C, 54.97; H, 3.52; N, 13.36.

Example 30

2-(5-Bromo-2-hydroxyphenyl)-3-(2-methyl-3-oxo-2,3-dihydro-pyridazin-6-yl)phenylpyrazolo[1,5-a]pyridine (358 mg, 61.7 %) was prepared by a procedure similar to that of Example 3.

mp 250-255℃ (EtOH);

FT-IR (KBr) 3087.5, 1656.6, 1575.6, 1529.3, 1496.5, 1477.2,
1423.2 cm $^{-1}$;

^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3H), 6.82-6.91 (m, 2H),
7.00-7.15 (m, 2H), 7.40-7.60 (m, 3H), 8.13(d, 1H, J = 8.9 Hz),

8.78 (d, 1H, J = 6.9 Hz), 9.99 (s, 1H);
(+)-APCI/MS m/z 397, 399 $(M+H)^+$;
Anal. Calcd for $C_{18}H_{13}Br_4O_2$: C, 54.43; H, 3.30; N, 14.10.
Found: C, 54.37; H, 3.22; N, 13.90.

Example 31

2-(5-Bromo-2-hydroxyphenyl)-3-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazolo[1,5-a]pyridine (480 mg, 71.4 %) was prepared by a procedure similar to that of Example 4.
mp 259.5-261.5℃ (EtOH);
FT-IR (KBr) 3147.3, 3093.3, 3047.0, 1662.3, 1585.2, 1531.2, 1510.0, 1475.3, 1419.4 cm^{-1};
^1H NMR (DMSO-d_6) δ 6.78-6.90 (m, 2H), 7.00-7.18 (m, 2H), 7.38-7.59 (m, 3H), 7.89 (d, 1H, J = 8.9 Hz), 8.78 (d, 1H, J = 6.9 Hz), 9.99 (s, 1H), 12.98 (s, 1H);
(+)-APCI/MS m/z 383, 385 $(M+H)^+$;
Anal. Calcd for $C_{17}H_{11}BrN_4O_2 \cdot 0.5\ H_2O$: C, 52.06; H, 3.08; N, 14.28.
Found: C, 52.46; H, 3.33; N, 13.90.

Example 32

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine (625 mg) as a pale yellow solid was prepared by a procedure similar to that of Example 2.
mp 153-155℃ (EtOAc);
FT-IR (KBr) 1662, 1631, 1597, 1537, 1514, 1473, 1456 cm^{-1};
^1H NMR ($CDCl_3$) δ 1.45 (d, 6H, J = 6.6 Hz), 3.59 (s, 3H), 5.42 (sep, 1H, J = 6.6 Hz), 6.72 (d, 1H, J = 9.6 Hz), 6.85-7.02 (m, 3H), 7.02 (t, 1H, J = 7.4 Hz), 7.26-7.35 (m, 1H), 7.41-7.50 (m, 1H), 7.59 (dd, 1H, J = 7.4, 1.7 Hz), 8.10 (d, 1H, J = 9.0 Hz), 8.53 (d, 1H, J = 7.0 Hz);
(+)-APCI/MS m/z 361 $(M+H)^+$;
Anal. Calcd for $C_{21}H_{20}N_4O_2 \cdot 0.25\ H_2O$: C, 69.12; H, 5.66; N, 15.35.
Found: C, 69.11; H, 5.55; N, 15.24.

Example 33

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyridine (1.32 g, 55.7 %) was prepared by a procedure similar to that of Example 2.

mp 112-113℃ (EtOH);

FT-IR (KBr) 1655, 1589, 1535, 1525, 1469 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.49 (d, 6H, J = 6.6 Hz), 3.87 (s, 3H), 5.44 (sep, 1H, J = 6.6 Hz), 6.76 (d, 1H, J = 9.6 Hz), 6.85-7.06 (m, 4H), 7.25-7.35 (m, 1H), 7.55 (d, 2H, J = 8.5 Hz), 7.98 (d, 1H, J = 8.9 Hz), 8.52 (d, 1H, J = 7.0 Hz);

(+)-APCI/MS m/z 361 $(M+H)^+$;

Anal. Calcd for $C_{21}H_{20}N_4O_2 \cdot 0.3\ H_2O$: C, 68.95; H, 5.68; N, 15.32.
Found: C, 68.94; H, 5.73; N, 15.35.

Example 34

2-(2-Hydroxyphenyl)-3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (257 mg) as a pale yellow solid was prepared by a procedure similar to that of Example 3.

mp 208-209℃ (EtOH);

FT-IR (KBr) 1645, 1572, 1531, 1496, 1477, 1448 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.49 (d, 6H, J = 6.6 Hz), 5.46 (sep, 1H, J = 6.6 Hz), 6.80-7.00 (m, 3H), 7.10-7.20 (m, 2H), 7.25-7.40 (m, 3H), 7.88 (d, 1H, J = 9.0 Hz), 8.51 (d, 1H, J = 6.9 Hz), 10.00 (s, 1H).

(+)-APCI/MS m/z 347 $(M+H)^+$;

Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17.
Found: C, 69.40; H, 5.17; N, 16.12.

Example 35

2-(3-Hydroxyphenyl)-3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (460 mg, 87.1 %) was prepared by a procedure similar to that of Example 3.

mp 259-260℃ (EtOH);

FT-IR (KBr) 1656, 1585, 1531, 1464, 1417 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.47 (d, 6H, J = 6.6 Hz),

5.41 (sep, 1H, J = 6.6 Hz), 6.76 (d, 1H, J = 9.6 Hz),
6.88-6.96 (m, 2H), 7.05-7.16 (m, 3H), 7.25-7.36 (m, 3H),
8.00 (d, 1H, J = 8.9 Hz), 8.53 (d, 1H, J = 7.0 Hz),
10.00 (s, 1H).
(+)-APCI/MS m/z 347 $(M+H)^+$;
Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17.
Found: C, 69.56; H, 5.20; N, 16.21.

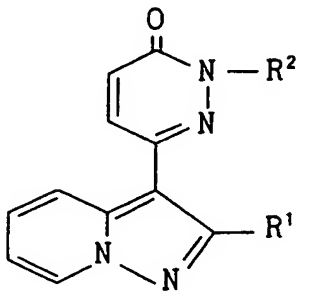
Example 36

2-(4-Hydroxyphenyl)-3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazolo[1,5-a]pyridine (312 mg, 58.2 %) was prepared by a procedure similar to that of Example 3.
mp 209-210℃ (EtOH);
FT-IR (KBr) 1662, 1587, 1496, 1471, 1444, 1419 cm^{-1};
^1H NMR ($CDCl_3$) δ 1.52 (d, 6H, J = 6.6 Hz),
5.47 (sep, 1H, J = 6.6 Hz), 6.79 (d, 1H, J = 9.6 Hz),
6.85-6.98 (m, 3H), 7.08 (d, 1H, J = 9.6 Hz), 7.25-7.36 (m, 1H),
7.44 (d, 2H, J = 8.5 Hz), 8.00 (d, 1H, J = 8.9 Hz),
8.53 (d, 1H, J = 6.9 Hz), 8.87 (s, 1H).
(+)-APCI/MS m/z 347 $(M+H)^+$;
Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17.
Found: C, 69.62; H, 5.20; N, 16.16.

This application is based on application No. PP6721/98 filed in Australia, the content of which is incorporated hereinto by reference.

CLAIMS

1. A pyrazolopyridine compound of the following formula (I):



(I)

wherein

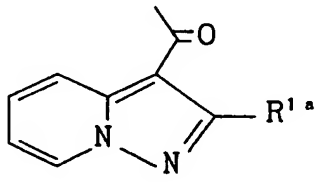
R^1 is a phenyl having one or two substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, hydroxy, lower alkoxy and ar(lower)alkoxy; and

R^2 is a hydrogen or a lower alkyl,

or a salt thereof.

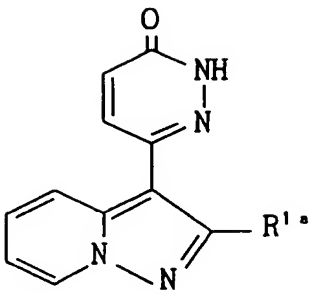
2. A process for the preparation of the pyrazolopyridine compound of claim 1 or a salt thereof, which comprises,

(1) subjecting a compound of the formula (II):



(II)

wherein R^{1a} is a phenyl having one or two substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, lower alkoxy and ar(lower)alkoxy, or a salt thereof, to cyclization reaction, to give a compound of the formula (Ia):



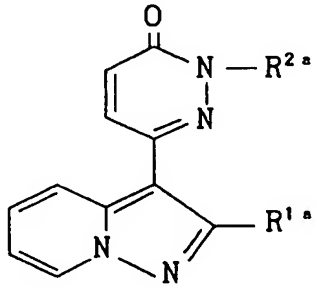
(Ia)

wherein R^{1a} is as defined above, or a salt thereof,

(2) reacting a compound of the formula (Ia) or a salt thereof, with a compound of the formula (III):

$$X\text{-}R^{2a} \quad (III)$$

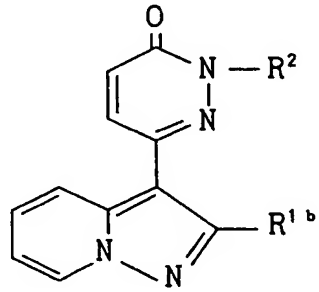
wherein R^{2a} is a lower alkyl and X is a leaving group, to give a compound of the formula (Ib):



(Ib)

wherein R^{1a} and R^{2a} are each as defined above, or a salt thereof,

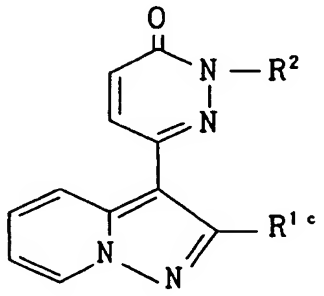
(3) subjecting a compound of the formula (Ic) :



(Ic)

wherein R^{1b} is a phenyl having one or two lower alkoxy and optionally having one or two substituent(s) selected from the group consisting of halogen, lower alkyl and halo(lower)alkyl, R^2 is as defined in claim

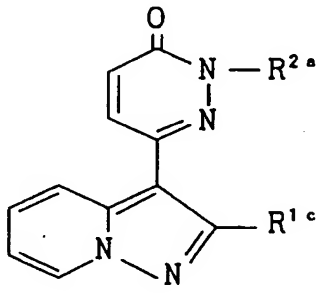
1, or a salt thereof, to elimination reaction of alkyl group, to give a compound of the formula (Id):



(Id)

wherein R^{1c} is a phenyl having one or two hydroxy and optionally having one or two substituent(s) selected from the group consisting of halogen, lower alkyl and halo(lower)alkyl, and R^2 is as defined in claim 1, or a salt thereof, or

(4) reacting a compound of the formula (Ie)

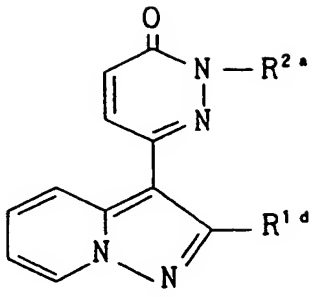


(Ie)

wherein R^{1c} and R^{2a} are each as defined above, or a salt thereof, with a compound of the formula (IV):

$$X\text{-}R^3 \qquad (IV)$$

wherein R^3 is a lower alkyl or an ar(lower)alkyl and X is a leaving group, to give a compound of the formula (If):



(If)

wherein R^{1d} is phenyl having one or two substituent(s) selected from the group consisting of lower alkoxy and ar(lower)alkoxy and optionally having one or two substituent(s) selected from the group consisting of halogen, lower alkyl and halo(lower)alkyl, and R^{2a} is as defined above, or a salt thereof.

3. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

4. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris, which comprises administering the compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an

animal.

5. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

6. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof as an adenosine antagonist.

7. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof as an A_1 receptor and A_2 receptor dual antagonist.

8. A process for preparing a pharmaceutical composition which comprises admixing the compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

9. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the therapy of diseases on which an adenosine antagonist is therapeutically effective.

10. A method for evaluation of adenosine antagonism which comprises use of compound of claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 99/05696

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/50 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP 0 379 979 A (FUJISAWA PHARMACEUTICAL CO) 1 August 1990 (1990-08-01) cited in the application page 12; examples 4,28,29	1-10
Y	WO 95 18128 A (FUJISAWA PHARMACEUTICAL CO ;AKAHANE ATSUSHI (JP); NISHIMURA SHINTA) 6 July 1995 (1995-07-06) see page 14, meaning of aryl (R1)	1-10
Y	WO 98 03507 A (KURODA SATORU ;AKAHANE ATSUSHI (JP); ITANI HIROMICHI (JP); SHIMIZU) 29 January 1998 (1998-01-29) see page 20, meaning of aryl (R1)	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 2000	02/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

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INTERNATIONAL SEARCH REPORT

Inte. nal Application No
PCT/JP 99/05696

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 102 878 A (KATAYAMA HIROHITO ET AL) 7 April 1992 (1992-04-07) see column 11, meaning of aryl (R1), see also examples	1-10

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